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The effect of acupuncture on the inflammatory response and spasticity following spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) is a serious pathological condition, which causes significant morbidity and mortality in patients who are suffering from it. Acupuncture is an important and integral part of traditional Chinese Medicine, which has been practiced in Asian countries for more than 5,200 years. The present narrative literature review aims to present recent research data in relation to the therapeutic effect of acupuncture on patients with SCI, and more specifically on the reduction of the inflammatory response and the spasticity after an injury of the spinal cord.

It seems that acupuncture, through its anti-inflammatory effect, is effective in patients with SCI. This therapeutic effect is multifactorial, including the regulation of the activity of various endogenic biological mediators, the regeneration of nerve fibres and stem cells and the inhibition of inflammation, neural apoptosis and oxidative stress in the injured spinal cord.

Since there is evidence that inflammation plays an important role in the spasticity seen in patients with SCI, there is necessity for future research, both at the experimental and also at the clinical level, in order to test the hypothesis of a close correlation between the anti-inflammatory effect of acupuncture and the successful treatment of spasticity in patients with SCI.

Key words: Spinal cord injury, Inflammation, Spasticity

Introduction

Spinal cord injury (SCI) is a particularly serious pathological condition, which causes significant morbidity and mortality in patients who are suffering from it, the incidence of the condition, on an annual basis, is estimated to be in the range between 8 and 246 cases / 1,000,000 people, with the total number of patients worldwide, estimated to be between 236 – 1,298 / 1,000,000 people [1]. In the U.S.A. alone, for the year 2012, the number of patients with SCI is estimated in the range of 25,000 – 1,275,000, with the relative trend showing a continuous increasing prevalence rate [2]. Since SCI can cause transient to permanent dysfunction of the nervous, urinary and musculoskeletal system leading to enormous psychological, economic and social burden, its successful treatment and rehabilita-

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tion strategy is mandatory [3].

There are two main stages following acute SCI: (i) the primary phase, immediately following injury, where destruction of the neural parenchyma, disruption of the neuraxonal network, bleeding in the injured area, and disruption and disorganization of the neuroglial membrane occur and (ii) the secondary phase which reflects a series of complex pathophysiological processes, occur immediately after the primary lesion, and evolve over the following several weeks triggering a "cascade" of inflammatory processes, with immediate activation of innate immune responses, demyelination, apoptosis of the oligodendrocytes, degeneration of the axons and finally apoptosis (death of the neurons) [4-10].

One of the most frequently occurring complications of SCI that significantly impairs patients' clinical condition and function is spasticity [11], which is estimated to occur in up to 70% of patients surviving after a serious SCI [12]. Spasticity can be either localized, regional or general and according to the European working group EUSPAM is defined as the "disordered sensorimotor control resulting from an upper motor neuron lesion and presenting as intermittent or sustained involuntary muscle activation [13,14]. Scientific research in recent years has also focused on inflammation as one of the causes of persistent spasticity in patients after severe SCI [15]. After all, there is already evidence that the combination of inflammation and neuronal destruction plays an important role in the development of spasticity in pathologic conditions such as multiple sclerosis, transverse myelitis or even in rarer diseases characterised by significant spasticity, such as the HTLV-1-associated myelopathy / tropical spastic paraparesis [16-23].

Acupuncture is an important and integral part of traditional Chinese medicine, [24], with a continuous increasing popularity on the treatment and management of painful pathological conditions [25-32].

The present narrative literature review provides recent research data in relation to the therapeutic effect of acupuncture on patients with SCI and on the reduction of the inflammatory response and spasticity following spinal cord injury. An extensive literature research was conducted in PubMed/NCBI, Cochrane Library and Goggle Scholar online databases. The mesh-terms used were: *Spinal cord injury, Acupuncture, Spasticity, and Inflammation* in various combinations and using the disjunctive terms AND and OR. The inclusion criteria were: original studies (both clinical and experimental) in humans and animals, published since 2005. Figure 1 presents the flow-chart of the review, according to the principles of PRISMA

Discussion

Of the 611 studies originally screened, 29 were finally included for further analysis. Literature data supports that acupuncture may improve patients' sensory and motor dysfunction, decrease the level of pain, improve bowel function, alleviate the neurogenic bladder symptoms, improve pressure ulcers outcomes, demonstrate a positive effect on post-injury osteoporosis and finally improve SCI-induced myospasms and spasticity [33-37]. The above mentioned therapeutic actions of acupuncture are multifactorial and include: (i) regulation of the activity and expression of various endogenic biological mediators, (ii) promotion of the regeneration of nerve fibers and stem cells, thus improving the neuroplasticity and (iii) combination of inhibition of inflammation, inhibition of neural apoptosis and decrease of the oxidative stress in the affected area of the spinal cord [33].

Furthermore, Cai and Shen [38] directly correlated the antiapoptotic mechanism of action of acupuncture in various neurologic diseases with the anti-inflammatory action of the therapeutic method, for example through the inhibition of the activation of the MAPK/ERK and P13K/Akt, the down-regulation of caspase-3 and cytochrome c expression on the spinal cord, along with the down-regulation of the serum TNF-αcontent [39-41]. Finally, in another more recently published literature review, Tang et al. (2020) [42] presented a direct correlation between the anti-inflammatory effect of acupuncture after SCI and the therapeutic effect noticed on post-injury nerve recovery after mesenchymal stem cells transplantation.

The therapeutic effect of acupuncture on inflammation following spinal cord injury

Regarding the therapeutic effect of acupuncture on the inflammatory processes that follow SCI, a number of experimental studies published in the last decade

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have shown very promising findings. Choi et al. published the first proof of the neuroprotective effect of acupuncture after SCI in an experimental rat model. The authors reported statistically significant reduction in the activity of microglia, p38 MAPK and 3 pro-inflammatory factors, including TNF-α, IL1-β, IL-6, matrix-metalloprotease-9 and cycloxygenase-2 [43]. Three years later, Lee et al. showed in a rat experimental model, that acupuncture after a SCI produces significant anti-inflammatory activity in both astrocytes and activated microglia, primarily through the inhibition of the activation of JNK (Jun-N—terminal kinase) [44]. Renfu et al., in an experimental trial on New Zealand rabbits, showed that the effectiveness of acupuncture in the treatment of SCI is most probable due to the regulation of the Pl3-K/Akt and MARK signaling pathways, which are directly related to the cell survival and apoptosis in the first stages of an acute SCI [45]. In another experimental rat model, after severe spinal cord compression, Nascimento de Souza et al., showed that bee venom acupuncture, applied at acupoints GV3 and ST 36, increased the anti-inflammatory expression of IL-10 just six hours after treatment and decreased the pro-inflammatory expression of IL-6 to the treatment group, in comparison to the control group. The final clinical outcome of the study was that the participants in the treatment group showed a statistically significant improvement in their locomotor performance and a reduction in the final extent of SCI compared to participants in the control group [46].

Spinal cord ischemia reperfusion injury (also referred as "white cord syndrome") is a rare pathological condition whose exact pathophysiology is not yet fully understood and which is characterized by acute SCI (paraplegia or quadriplegia), after surgical procedures of spinal decompression [47]. Fang et al. showed that the application of electroacupuncture, either before or after the procedure could alleviate the ischemia of the spinal cord, mainly due to the neuro-anti-inflammatory effect of the method (mainly due to the decreased expression of TNF-αand IL-1β) [48]. Another experimental model involving rats with SCI showed that yellow laser stimulation at GV2 acupoint resulted in an enhanced recovery of the injured spinal cord, mainly due to the down-regulation of a number of pro-inflammatory factors and cells, including the polymorphonuclear leucocytes, the COX-2, the BAX and the Caspase-3 [49]. The effect of acupuncture on the pathophysiological mechanism of Caspase-3 in various tissues, has been already shown by Du et al. (2013) [50] on rabbits, through the Fas-Caspase-3 cascade pathway. On the other hand, Shi et al. (2016), presented the role of apoptosis-regulator BAX protein (also known as bcl-2-like protein 4) in rats with moderate degree of SCI. The authors showed that animals treated with needle therapy at ST28 and BL54 acupoints presented recovery from acute SCI through a neuroptotective and anti-inflammatory effect [40].

The anti-inflammatory effect of acupuncture in SCI was recently demonstrated in another experimental study by Dai et al. (2021), showing that electroacupuncture treatment after SCI in mice, protected myelinated axons and neurons through a complex mechanism which down-regulated the pro-inflammatory cytokines, while it up-regulated anti-inflammatory cytokines. The most probable pathway of this anti-inflammatory effect was mediated through an apolipoprotein-E (apo-E) dependent mechanism [51]. Jiang et al. summarized the anti-inflammatory effect of acupuncture after severe SCI. The researchers applied three different modalities of acupuncture (transcutaneous acupoint electrical stimulation, manual acupuncture and electoacupuncture) at DU26 and DU16 acupoints, in 110 rats in order to study the neuroprotective effects of the methods. The researchers found a statistically significant reduction of a number of inflammatory cytokines, including IL1-β, IL-6 and TNF-α. In addition, the antioxidant action of acupuncture was confirmed by the reduction of the activity of both superoxide dismutase (SOD) and malondialdehyde (MDA) immediately after the injury. They concluded that therapeutic intervention with acupuncture at DU26 and DU16 acupoints immediately after SCI, offers significant neuroprotective action and increased neuronal recovery, through a complex antioxidative, anti-inflammatory and anti-apoptotic mechanism [52].

The non-inflammatory therapeutic effect of acupuncture following SCI

During the last few years, a number of experimental animal studies have been published demonstrating the efficacy of acupuncture on SCI, by mechanisms

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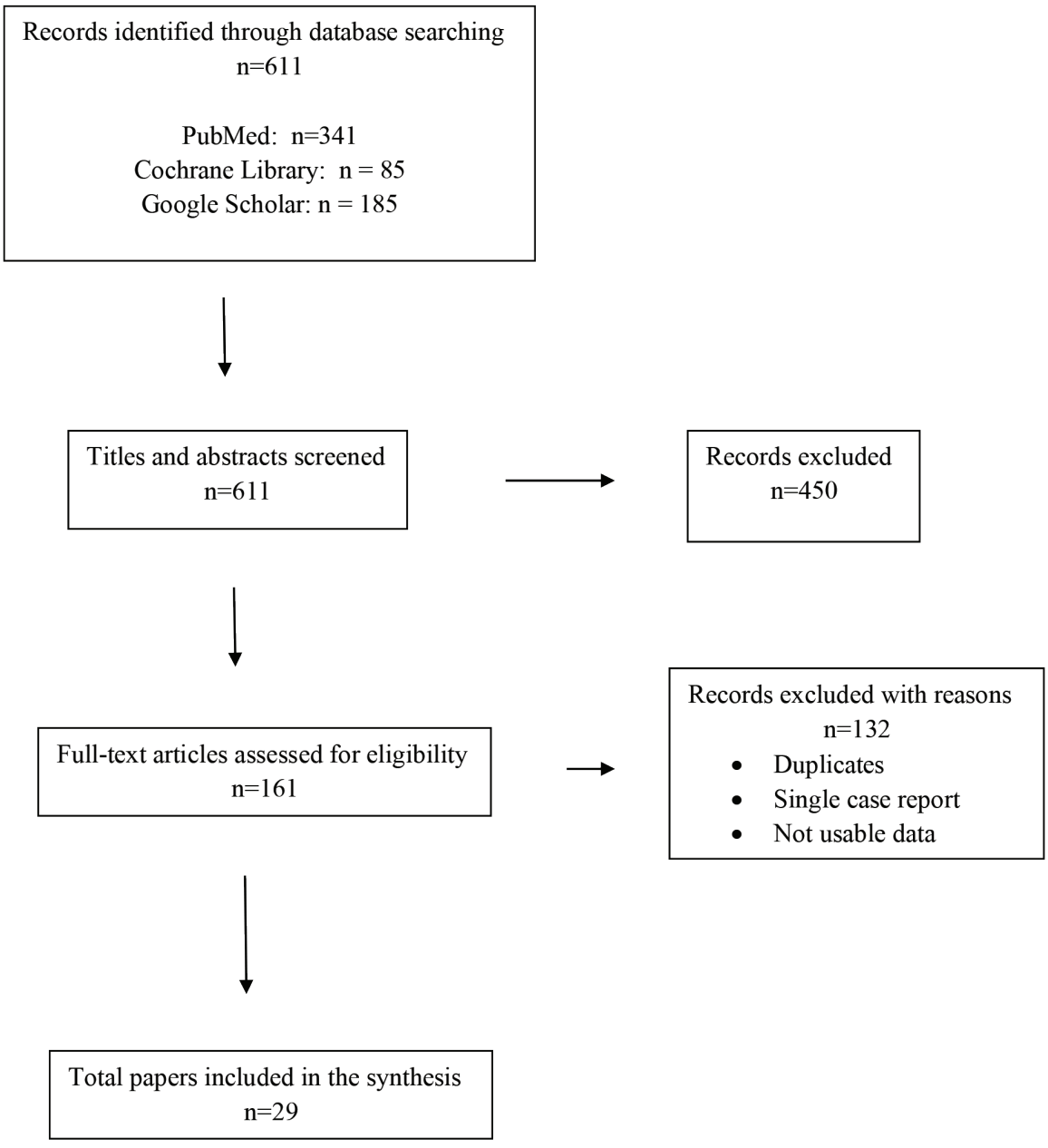

Figure 1: The PRISMA flow-diagram of the present literature review.

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other than the direct anti-inflammatory action.

Huang et al., in an experimental model of c SCI injury in rats, showed that just 14 days of electoacupuncture treatment at Kl3 and ST36 acupoints produced both locomotor improvement and improvement of the ultrastructural features of the myelin sheath in the affected area of the spinal cord, through the inhibition of the death and the promotion of the proliferation of the oligonedrocytes [53].

Zhou et al. (2020) studying the effect of acupuncture on the abnormal microRNA (miRNA) expression on 6 rats, showed that in the treatment group (elecroacupuncture) the apoptotic indices were lower in comparison to the control group [54]. Yang et al. reported that electoacupuncture on SCI rats increased the acetylcholinesterase (AChE) activity, upregulated of glial cell line-derived neurotrophic factor mRNA (GDNF mRNA) expression, with the end result being the functional recovery of the anterior horn motor neurons [55].

In the last decade, the effect of acupuncture on the regeneration of nerve fibers and differentiation of mesenchymal stem cells has been studied. Yan et al. showed that electoacupuntcure treatment, seven days after SCI induction on rats, produced an increase of the endogenous neutrophin-3 (NT-3) at the injured area, promoting mesenchymal stem cells differentiation into oligodendrocyte-like cells and neuronal-like cells [56]. Similar findings were also presented by an experimental study published two years earlier, showing that acupuncture promotes both the differentiation and the survival of bone marrow mesenchymal cells of rats after induced SCI [57]. The most likely mechanism of this action is an increase in the levels of cAMP and neurotrophin-3 (NT-3), with the final result being the stimulation of the axonal growth in the area of the SCI and the improvement of the rat's hind limb locomotion.

Finally, Liu and Wu demonstrated the anti-apoptotic action of electroacupuncture through a combination of : (i) down-regulation of a number of pro-apoptotic proteins, including cleaved-caspase-3, cleaved caspase-9 and cleaved PARP, (ii) up-regulation of the anti-apoptotic protein Bcl-2, (iii) up-regulation of a large set of miRNAs, from which the most significant was the miR-214, and finally, (iv) up-regulation of BAX protein (bcl-2-like protein and Nav 1.3 voltage-gated sodium channels [58]. These combined mechanisms, involving both inflammatory and non-inflammatory pathways, were also presented in the study of Li et al. where the researchers found that among 15 proteins whose levels changed after acupuncture, two of them (annexin A5 and collapsin response mediator protein 2) might be the most important neural specific factors concerning the therapeutic effects of electroacupuncture after SCI, in an number of pathways, including inflammation, migration and adhesion of neural cells, and apoptotic and signal transduction processes [59].

Conclusion

Acupuncture is an alternative therapeutic method that has been applied for thousands of years to a large number of patients and a variety of pathological conditions. Through its anti-inflammatory effect, it appears to be effective in patients with SCI. As there is evidence that inflammation plays an important role in the development of spasticity in patients with SCI, it is necessary for future research, both at the experimental (in vitro) and clinical (in vivo) level, to test the hypothesis of a close correlation between the anti-inflammatory effect of acupuncture and the successful treatment of spasticity.

Conflict of Interest

"The authors declared no conflicts of interest".

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